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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/360,242	07/22/1999	JOHN R. MCDONALD	25020-601B	3887

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EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/360,242	MCDONALD ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *26-29,31,32,34-38,40,42,44-54,57 and 65-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29,31,32,34-38,40,42,44-54,57 and 65-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/19/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. The Amendment, filed 7/28/03, has been entered into the record. Claims26-29, 31, 32, 34-38, 40, 42, 44-46, 48-54, 57 and 65-91 are pending and are the subject of this Office Action.

B. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

A. Claims 26-29, 31, 32, 34-38, 40, 42, 44-46, 48-54, 57 and 65-91 remain rejected under 35 USC 112, first paragraph for the reasons already of record on pages 2-4 of the Office Action dated 1/15/03. Applicants argue that the Declaration by John McDonald should be found persuasive since the specification must teach one of skill in the art to make and use that which is claimed, which the instant specification does. Applicants argue that the Declaration does not teach how to make and use what is claimed, but was provided to demonstrate that the conjugates function as claimed in light of the apparent doubt expressed by the Examiner. Applicants further argue that there is no requirement for an application to address future rejections or to provide in vivo data.

These arguments have been considered, but are not deemed persuasive. Respectfully, the application does not teach how to make and use what is claimed. The claims are drawn to a method of treating the underlying pathology of inflammatory responses. This method is performed *in vivo*. However, **the breadth of these claims is excessive**. The specification only discloses the use of OPL98110 on a RIP assay and on migrating target cells in vitro (Example 2). **The specification does not provide any guidance or working examples of how to make and use toxin-chemokine conjugates** for their claimed use in vivo. In the Declaration filed 10/25/02, Applicant does provide data on three of the conjugates. However, OPL98110 is only used in vitro whereas OPL98111 is used both in vitro and in a mouse xenograft model. However, the use of the xenograft model only demonstrates that OPL98111 can be used to retard tumor growth relative to control animals and that it has an anti-angiogenic effect. Furthermore, tumors are not inflammatory diseases and it is not clear how the treatment of tumors using the claimed conjugates can be enabling for the treatment of actual inflammatory diseases. OPL98112, on the other hand, was used in vitro and in vivo, but the in vivo results only show that the compound is not toxic. There is no data demonstrating that these compounds act as desired in the claimed invention; that is, by affecting the underlying inflammation in any and all inflammatory diseases. Applicants have only

demonstrated that the compounds disclosed in the Declaration can distinguish between activated and quiescent cells and that activated, proliferating and migrating cells should be eliminated. Nothing in the Declaration demonstrates that this is occurring, or would occur, *in vivo* to treat the claimed pathologies. In other words, the examples in the specification and Declaration do not use an art-accepted model for treating even one inflammatory disease. While Applicants are correct that the application does not need to address future rejections, Applicants have still not overcome the bar for enablement under 35 USC 112, first paragraph, regarding undue experimentation.

The Declaration further states that "in tissues treated with OPL98111 and harvested immediately for examination, there was a stark lack of monocytic cells in necrotic regions. When treated tissues were harvested after treatment was withdrawn (1 day), monocytic cells were once again detected. It can be concluded that OPL98111 eradicated the monocytic cells..." The Declaration concludes that the mouse host is the origin of the endothelial and monocytic cells since only a tumor cell-line was used to inoculate the mice and that the cells must have been activated, proliferating and migrating in order to invade the tumor tissue.

This argument has also been considered, but is not deemed persuasive. First, the experiment focuses on the treatment of a tumor. OPL98111 inhibited tumor growth and, according to Applicants' specification, OPL98111 should have inhibited active monocytes. However, it is not understood how the activated monocytes played a role in tumor progression. It is clear that the infiltration of monocytes into a tumor could inhibit tumor growth, but it is not clear how inhibition of these cells into a tumor can prevent tumor growth. Again, tumors are not inflammatory diseases and it is not clear how the treatment of tumors using the claimed conjugates can be enabling for the treatment of actual inflammatory diseases

Applicants argue that, as taught in the Declaration and specification as filed, the instant methods are based upon treatment of a common underlying pathology that is shared by a variety of disorders and that the methods target immune effector cells involved in these pathologies. In other words, the claims are not drawn to treating all pathologies, but to modulating the activity of immune effector cells which are involved in a variety of pathological conditions. Applicants argue that it is clear from the art that numerous different disorders share this common underlying pathology. Applicants argue that the specification does teach the artisan how to select, prepare and administer chemokine targeting agents for particular diseases and stages thereof and that the specification is presumed enabled even in the absence of working examples. Applicants further argue that the specification provides a generic treatment modality for treating this underlying pathology and there is no need for Applicants to disclose every species falling within this generic invention and the specification teaches how to practice the methods as

claimed. Applicants argue that "there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims [which] are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which applicant has disclosed." While this statement may be true, it does not summarize the present situation. The only data provided is that of a mouse xenograft model which demonstrates the effectiveness of these compounds on a tumor. This is not probative since it is not clear that the conjugates are affecting the underlying cause of tumor progression, as claimed in the present invention. Even, arguendo, this was an adequate example of the claimed methods, **Applicants still have not provided a representative number of examples of treating inflammatory diseases using art-accepted models**. As stands, this application, respectfully, represents a research project and an "invitation to experiment."

In Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), the court held that:

> "*[u]nless and until a process is refined and developed to th[e] point - where specific benefit exists in* currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicants have an idea, but have not provided sufficient support to demonstrate that their idea is functional (i.e. enabled) in a true in vivo model system of inflammation. While it is true that Applicants have disclosed a general treatment modalitly (i.e. a generic invention) this general modality is not enabled, **nor, again, have they provided a representative number of examples to enable their invention**.

These other arguments are also not deemed persuasive. First, respectfully, treating a disease and treating the underlying pathology of the disease is a matter of semantics. It is not understood how Applicants are *not* treating the disease when they are treating the underlying pathology of a disease. Regardless of how the claim is worded, it appears that Applicants are encompassing a method of treating these diseases. Claim 29 reads, for example, treating the pathology underlying "neurodegenerative disorders." This would include Parkinson's disease, Alzheimer's and Down's syndrome." In fact, a "short" list of diseases which, according to Applicants, would be expected to be treated include such unrelated diseases as spinal cord injury, stroke, acute lung injury, acute respiratory distress syndrome, inflammatory joint diseases such as rheumatoid arthritis, HIV encephalitis, neovascularization, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis, Chron's disease, proliferative vitreoretinopathy and uveitis (see pages 152-153 of the specification). It is well-known in the art that this wide variety of diseases are not caused by the same underlying immune response, nor would it be expected that, due to the complexity of the immune system, a "simple" method of treatment using

conjugates would be effective in treating these distinct diseases **without further guidance and working examples**. Furthermore, the specification does not teach the artisan how to select, prepare and administer chemokine targeting agents for particular diseases and stages thereof. The specification simply discloses the basic fact that "the artisan can select, prepare and administer chemokine targeting agents for particular diseases and stages thereof, (as seen in Tables 1-6 of the specification)," **but does not provide any significant guidance of how to do so**. If this information is so basic that the specification does not need to teach specific examples, then it is not clear why neither the specification, nor the Declarations, provide examples of diseases (or underlying pathologies) being treated. It would seem to reason that if this information (i.e. treatment regimen) were, respectfully, as simple **and as predictable** as the specification, Declarations and Applicants' arguments make it appear, then showing that these diseases were actually treated would have been disclosed in the specification. It is apparent that, in fact, the ability to treat a disease by treating the underlying pathology **is not as simple or as predictable** as the specification and Declarations make it appear. Inflammatory disease states are complex and Applicants are basically saying "here are known chemokines and cytokines. Use them however you can to treat any disease, and alter the regimen as you see fit when the stage of the disease progresses, but we are not going to tell you how to do this, since the chemokines and toxins are so well known." This is not adequate disclosure for enablement, **nor would this information make it predictable** to the artisan how to make and use the conjugates to practice the claimed methods.

Applicants argue that "when one skilled in the art would accept a particular test or experiment as being reasonably predictable that a tested invention would operate as alleged or have a therapeutic effect as alleged, the burden on behalf of an applicant has been satisfied." While Applicants may teach the chemokine system in detail, and an example of which receptors are present on certain cells at certain stages of disease progression, since this is known in the art, this "how to make and use the claimed invention" (i.e. conjugates) does not teach any more than the prior art discloses and this plethora of pages in the disclosure of how to make and use the conjugates is not a substitute for an enabling specification. Applicants state that in the IDrugs paper, Dr. McDonald states that they "suggest that specific chemokine-toxins would be effective in treating a wide array of conditions..." but this is merely a suggestion. The paper further discloses that "...this variation in chemokine level and target cell level can be exploited in the claimed methods to finely tune treatment for a particular disease. However, this is a "wish to achieve", not an accomplishment. A person of ordinary skill in the art would not find it credible to treat all diseases, or the underlying pathology, based on the teachings of the specification, **nor would the artisan consider this approach predictable**. A person of ordinary skill in the art would not find it credible to treat all

diseases, or the underlying pathology, based on the teachings of the specification. **Given the wide range of disease and the complexity of disease states, along with a lack of guidance and working examples of functional conjugates, it would not have been predictable to one of ordinary skill in the art at the time of the present invention to have known which conjugates to use for a particular disease at a particular stage of the disease**, or what the effects and side-effects of these conjugates would be. Applicants are basically using a "blanket" approach or a "magic principle" and leaving it up to the individual artisan to determine which conjugates will work under which conditions, under which diseases and under which stages of these diseases. In other words, respectfully, Applicants are leaving it up to the artisan to complete the required research for Applicants' desired patent. As taught by Benjamini et al (*In* Immunology:A short course, 3rd. ed. 1996) "Given the complexity of the immune response and its potential for inducing damage, it is self-evident that it must operate under carefully regulated conditions." Therefore, it would stand to reason that great care must be taken when choosing how and when to use the claimed conjugates to affect the immune system. The artisan cannot just assume that any conjugate will work as predicted under all circumstances, especially given the wide variety of circumstances (i.e. diseases). It is apparent that determining the effect of the conjugates on a patient would involve more than simply determining the toxicity of a particular conjugate, or believing that it is as simple as targeting a desired cell population with the expectation of no unwanted side-effects. In other words, the issue is, respectfully, more complex than stating "here are the known chemokines and cells to which they bind – the treatment, therefore, is commonplace." Benjamini et al. is not being used as a new grounds of rejection, but simply to further support the Examiner's position that due to the complexity of the immune system, Applicants are not enabled for the scope of their claimed invention.

Therefore, in summary, the breadth of the claims is excessive with regard to Applicants claiming methods for treating the underlying pathology of all inflammatory responses. The specification does not provide any guidance or working examples of how to make and use toxin-chemokine conjugates for their claimed use in vivo, nor is it predictable to the artisan how to make and use the large number of conjugates available to treat the diverse types of diseases, or their underlying pathology, given what is taught in the specification. For these reasons, the Examiner maintains that undue experimentation would be required to practice the invention as claimed.

3. Claim Rejections - 35 USC § 102/103

A. All rejections under 35 USC 102/103 and 35 USC 103 have been withdrawn in view of Applicants' arguments and the Declaration under 37 CFR 1.132 by John McDonald which demonstrate that the fragment of MGSA/GRO-α does not bind chemokine receptors.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
November 20, 2003

Gary L. Kunz

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